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Klebsiella pneumoniae bacteraemia in a region of Canada

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Abstract

The second case of *magA*+ *rmpA*+ hypermucoviscosity phenotype *Klebsiella pneumoniae* infection was documented in Canada, in an immigrant from Algeria. To ascertain whether this represented recent importation of the strain or local transmission within Canada, a retrospective study of *K. pneumoniae* bacteraemia was conducted in the region, from 1997 to 2007, and 411 episodes were identified. No epidemiological evidence for local transmission of this strain was found. However, for the first time, the population incidence of *K. pneumoniae* bacteraemia was determined, which increased by 82% between 1997 and 2007, from 10.2 to 18.7 per 100 000 inhabitants. Incidence increased dramatically with age and with the presence of diabetes, but remained stable over time within each stratum. The proportion of patients with *K. pneumoniae* bacteraemia who were diabetic increased from 26% (1997–2004) to 42% (2005–2007). The rising incidence of *K. pneumoniae* bacteraemia may represent an unexpected consequence of the expanding population of adult diabetics.

Keywords: Bacteraemia, Canada, diabetes, incidence, *Klebsiella pneumoniae*
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Introduction

Klebsiella pneumoniae, a Gram-negative rod that forms large mucoid colonies owing to its polysaccharide capsule, causes a wide spectrum of community-acquired and nosocomial infections. Over the past two decades, a novel hypermucoviscosity (HV) phenotype of *K. pneumoniae*, characterized by the formation of elongated (>5 mm) mucoviscous strings when a loop is passed through the colony, has been described in Taiwan where, concomitantly, a distinctively invasive syndrome of bacteraemia with liver abscess emerged, sometimes complicated by meningitis, endophthalmitis or other metastatic suppurative foci [1–4]. This phenotype is associated with the *magA* (mucoviscosity associated gene A) and *rmpA* (regulator of mucoid phenotype) genes and the K1 serotype [3,5–7]. To our knowledge, this strain has not yet been reported in Europe. The first case in North America was diagnosed in a Filipino migrant who presented with a liver abscess [5]. Two more cases of Asian patients with a liver abscess were described in Texas and Manitoba [8,9]. We report the second case of infection with the *magA*+ *rmpA*+ strain of HV *K. pneumoniae* in Canada, in a patient who had recently migrated from Algeria, a country not known to have endemic HV *K. pneumoniae*. To ascertain whether this represented recent importation of the strain by the patient or local transmission within Canada, we conducted a retrospective study of *K. pneumoniae* bacteraemia in our region, looking for changes in the incidence, clinical characteristics and mortality attributed to this infection. This allowed us to document for the first time the epidemiology of *K. pneumoniae* bacteraemia at a population level. As diabetes mellitus is an important predisposing factor for infection with *K. pneumoniae*, including the HV phenotype and other strains [1,3], we paid particular attention to the role of this chronic disease in modulating the incidence of *K. pneumoniae* bacteraemia.

Case Report

The patient was a 47-year-old male asylum seeker, who allegedly travelled from Algeria to Canada 6 weeks prior to admission. He had been previously healthy except for type 2 diabetes mellitus, treated with oral hypoglycaemic agents. He

presented with a 3-week history of fever, dysuria and left thigh pain. He appeared toxic and jaundiced. His temperature was 39.5°C. Palpation of the inner thigh was painful with no apparent inflammatory signs. His prostate was enlarged and tender. His leucocyte count was 27.1×10^9/L, glycaemia 22.5 mmol/L, glycosylated haemoglobin 10.8%, and liver function tests showed cholestatic perturbations. Urine analysis showed leukocyturia and ciprofloxacin was started. A computed tomography (CT) scan of the abdomen and pelvis demonstrated two liver collections, the largest measuring 6.5×5.5 cm. The prostate was enlarged with multiple collections suggestive of abscesses. A CT scan of the left thigh showed a large abscess for which the patient underwent surgical drainage. Specimens from the thigh abscess, the percutaneous hepatic drainage, as well as from blood and urine, grew *K. pneumoniae* sensitive to ceftazidime, ceftriaxone, ciprofloxacin, gentamicin and carbapenems. The patient underwent a trans-urethral resection of the prostate. Ophthalmological evaluation did not reveal endophthalmitis. Hepatic drainage continued for 5 weeks. He was discharged with outpatient ertapenem. His clinical course was favourable. On blood agar, the *K. pneumoniae* isolate grew as hypermucoviscous colonies and displayed a positive string test. The organism was sent to the University of Washington where the *magA* and *rmpA* genes were detected by PCR [5].

Methods

Data collection

We reviewed all cases of *K. pneumoniae* bacteraemia diagnosed between January 1997 and December 2007 at the Centre Hospitalier Universitaire de Sherbrooke (CHUS), a 686-bed tertiary-care hospital in the province of Quebec, Canada. CHUS has the only microbiology laboratory in the city of Sherbrooke (population in 2007: 149 807); for this subpopulation, hospital data can be translated into population incidence. CHUS also provides secondary and tertiary care to a larger population. We searched the microbiology laboratory records and the hospital's computerized medical records to identify all patients in whom a *K. pneumoniae* bacteraemia had been documented. A patient could be included more than once if bacteraemic episodes occurred ≥30 days apart. Episodes of *K. pneumoniae* bacteraemia separated by less than a month were considered as relapses or persistence of the initial episode. Authorization for retrospective review of patients' records was granted by the hospital's director of professional services. Records were reviewed to collect: demographic information; presence of diabetes; immunosuppressive or systemic corticosteroid therapy; recent antibiotic use; recent surgical or invasive procedures; hospitalizations within the past year; underlying biliary or urinary tract anomalies; anatomical sources of infection; antimicrobial susceptibility test results and treatment.

Definitions and outcomes

Recent antibiotic exposure was defined as any antibiotic used for ≥48 h in the month preceding the bacteraemia. Invasive procedures included upper or lower endoscopy, endoscopic retrograde cholangio-pancreatography, nephrostomy or cystoscopy performed within 72 h before the bacteraemia. Nosocomial bacteraemia was defined as occurring >48 h after hospital admission or <14 days after discharge. Healthcare-associated bacteraemia included episodes in patients hospitalized in the previous year, residing in long-term care facilities, receiving chronic dialysis or cancer chemotherapy, or having an intravascular catheter or indwelling urinary catheter at home. All other episodes were considered community acquired. Biliary tract anomalies included lithiasis, stents or cholangiocarcinoma. Urinary tract anomalies included lithiasis, double-J ureteral stents, permanent indwelling catheter or ileal bladder. We considered intensive care unit (ICU) admission, use of vasopressors for septic shock and mechanical ventilation to be related to *K. pneumoniae* bacteraemia if initiated within 48 h of its onset.

The primary outcome was infection-related 30-day mortality. Secondary outcomes included ICU admission, septic shock, mechanical ventilation, all-cause mortality or relapses within 30 days of onset of bacteraemia. To determine whether mortality had been caused by *K. pneumoniae* bacteraemia or concomitant illnesses, we relied on physicians' notes in the days prior to death, discharge diagnoses, presence of other rapidly fatal conditions and whether aggressive supportive care had been provided.

Non-bacteraemic *K. pneumoniae* infection at selected sites

To identify non-bacteraemic infections potentially caused by HV *K. pneumoniae* at other sites, we identified through discharge diagnoses all cases of liver abscesses, bacterial meningitis and endophthalmitis during the same 1997–2007 period. Cultures of appropriate specimens were reviewed to determine the bacterial aetiology.

Population incidence

The measures of population incidence were restricted to cases occurring among inhabitants of Sherbrooke, for whom our institution is the only microbiology laboratory, capturing all cases of *K. pneumoniae* pneumonia within this subpopulation. To calculate the age-specific incidence among residents of Sherbrooke, census data from the Quebec Statistical Insti-

tute were used for denominators [10]. To stratify between diabetics and non-diabetics, the number of prevalent cases of diabetes within the same Sherbrooke population was estimated from the Med-Echo provincial hospital discharges database (any hospital admission with a diagnosis of diabetes, or one of 16 complications of diabetes) and from the database of the Régie d'Assurance-Maladie du Québec (at least two physician billings with a diagnosis of diabetes within the last 2 years). This algorithm has been validated and is widely used in Canada by the National Diabetes Surveillance System (NDSS) [11,12]. Residence in Sherbrooke was defined according to patients' postal codes. These measures of the prevalence of diabetes were available only for adults and for the period 1997–2004. Because in Quebec all medical care is paid for by the provincial government, and in Sherbrooke a single hospital provides inpatient care, we would also capture almost all patients diagnosed with diabetes.

Statistical analysis

Data were analysed with STATA 8.0 (StataCorp LP, College Station, TX, USA). Proportions were compared with the chi-square test or Fisher's exact test. Logistic regression was used for multivariate analysis of risk factors for mortality, and results are presented as adjusted odds ratios (AOR) with 95% confidence intervals (CI). Models were built up sequentially, starting with the variable most strongly associated with the outcome and continuing until no other variable reached significance. Then, each variable was dropped in turn to assess its effect. Different models were compared with the likelihood ratio test. We kept in the final model variables that significantly enhanced the fit at the $p \leq 0.05$ level. Interactions were sought between these variables.

Results

Table 1 shows the demographic and clinical characteristics of patients according to year of diagnosis. There was little change over time in the age and gender distribution, risk factors for *K. pneumoniae* bacteraemia or anatomical sources. Pyelonephritis and biliary tract sepsis were the most common sources. One-third of the patients were diabetic, but the prevalence of diabetes increased significantly in 2005–2007. Resistance to third-generation cephalosporins or ciprofloxacin remained very uncommon. There was no change in the severity of infection as measured by ICU admission, septic shock, need for ventilatory support, all-cause mortality and infection-related mortality. Demographic and clinical characteristics were similar in diabetic and non-diabetic patients (data not shown). During the period of observation,

TABLE 1. Characteristics of patients with *Klebsiella pneumoniae* bacteraemia, 1997–2007

	1997–2000 (*n* = 111)	2001–2004 (*n* = 169)	2005–2007 (*n* = 131)
Age, years (%)			
<18	2 (2)	4 (2)	9 (7)
18–64	29 (26)	46 (27)	43 (33)
≥65	80 (72)	119 (70)	79 (60)
Gender (%)			
Male	57 (51)	84 (50)	65 (50)
Female	54 (49)	85 (50)	66 (50)
Site of acquisition (%)			
Community	35 (32)	50 (30)	38 (29)
Healthcare associated	30 (27)	57 (34)	48 (37)
Hospital	46 (41)	62 (37)	45 (34)
Invasive procedure, last 72 h (%)	5 (5)	12 (7)	13 (10)
Underlying biliary tract anomaly (%)	40 (36)	66 (39)	50 (38)
Underlying urinary tract anomaly (%)	25 (23)	44 (26)	28 (22)
Diabetes mellitus (%)	31 (28)	42 (25)	55 (42)
Other pathogen in blood culture (%)	24 (22)	51 (30)	34 (26)
Antimicrobial resistance (%)			
Resistant to third generation cephalosporins	0 (0)	2 (1)	1 (1)
Resistant to ciprofloxacin	2 (2)	2 (1)	2 (2)
Sources (%)			
Pyelonephritis	31 (28)	60 (35)	43 (33)
Cholangitis/cholecystitis	33 (30)	42 (25)	38 (29)
Pneumonia/empyema	9 (8)	6 (4)	11 (8)
Liver abscess	1 (1)	1 (1)	3 (2)
Abscess at other sites	3 (3)	4 (2)	8 (6)
Other intra-abdominal infections	17 (15)	14 (8)	10 (8)
Soft tissue infections	1 (1)	5 (3)	2 (2)
Catheter sepsis/endovascular	7 (6)	12 (7)	15 (11)
Primary bacteremia (no source identified)	17 (15)	34 (20)	11 (8)
Outcomes (%)			
ICU admission	33 (30)	43 (25)	40 (31)
Septic shock	13 (12)	21 (12)	25 (19)
Need for mechanical ventilation	11 (10)	11 (6)	18 (14)
30-day mortality, all causes	17 (15)	24 (14)	22 (17)
30-day mortality attributed to *K. pneumoniae* infection	13 (12)	17 (10)	13 (10)
Recurrence of bacteremia within 30 days	2 (2)	5 (3)	5 (4)

p-Values >0.05 for all comparisons, excepted diabetes for which p 0.004.

no cases of *K. pneumoniae* meningitis or endophthalmitis occurred. There were five cases with bacteraemic *K. pneumoniae* hepatic abscess, and only two cases of non-bacteraemic liver abscess (one in 2002, the other in 2005). Of these seven cases, three occurred in the setting of cholangitis or cholecystis and one after Whipple's procedure for pancreatic cancer.

Table 2 shows the risk factors for infection-related mortality within 30 days of onset of bacteraemia. In multivariate analysis, the independent risk factors for infection-related mortality were hospital acquisition, polymicrobial bacteraemia, pneumonia as the source and lack of effective treatment within the first 24 h. When fitted into this model, diabetes mellitus was not associated with mortality (AOR: 1.17, 95% CI: 0.56–2.46, p 0.67).

Annual incidence of *K. pneumoniae* bacteraemia in Sherbrooke increased progressively during the study period, from 10.2 to 18.7 per 100 000 (Table 3). The increase in incidence was noted for community-acquired, healthcare-associated or

TABLE 2. Risk factors for infection-related mortality within 30 days of onset of *Klebsiella pneumoniae* bacteraemia, 1997–2007

	Infection related mortality/ total (%)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age, years			
<18	2/15 (13.3)	1.66 (0.33–8.43)	NS
18–64	10/118 (8.5)	1.00	
≥65	31/278 (11.2)	1.35 (0.64–2.85)	
Gender			
Female	21/205 (10.2)	1.00	NS
Male	22/206 (10.7)	1.04 (0.55–1.96)	
Site of acquisition			
Community	7/123 (5.7)	1.00	1.00
Healthcare-associated	12/135 (8.9)	1.63 (0.62–4.28)	1.42 (0.52–3.89)
Hospital	24/153 (15.7)	3.11 (1.29–7.48)[a]	2.99 (1.15–7.76)[a]
Systemic corticosteroids or immunosuppressive drugs			
No	33/357 (9.2)	1.00	NS
Yes	10/54 (18.5)	2.24 (1.03–4.86)[a]	
Underlying biliary tract anomaly			
No	33/255 (12.9)	1.00	NS
Yes	10/156 (6.4)	0.46 (0.22–0.96)[a]	
Underlying urinary tract anomaly			
No	38/313 (12.1)	1.00	NS
Yes	5/97 (5.2)	0.39 (0.15–1.03)	
Diabetes mellitus			
No	29/283 (10.2)	1.00	NS
Yes	14/128 (10.9)	1.08 (0.55–2.12)	
Other pathogen in blood culture			
No	24/302 (7.9)	1.00	1.00
Yes	19/109 (17.4)	2.42 (1.27–4.62)	2.44 (1.20–4.96)[a]
Sources			
Pyelonephritis[c]	7/132 (5.3)	1.00	1.00
Cholangitis/cholecystitis	9/113 (8.0)	1.53 (0.55–4.25)	1.66 (0.57–4.85)
Pneumonia	11/26 (42.3)	13.10 (4.41–38.89)[b]	12.35 (3.99–38.27)[b]
All other sources	6/76 (7.9)	1.53 (0.49–4.73)	0.90 (0.28–2.95)
No source identified	10/62 (16.1)	3.43 (1.24–9.51)[a]	2.13 (0.73–6.24)
Treatment within the first 24 h			
Effective antibiotics	34/367(9.3)	1.00	1.00
No effective antibiotic	9/42(21.4)	2.68 (1.18–6.07)[a]	2.59 (1.03–6.50)[a]

NS, not significant.
[a]$p < 0.05$.
[b]$p < 0.001$.
[c]For two patients with two sources, the source other than urine was used for analysis.

hospital-acquired infections. Incidence was much higher among elderly individuals: for the whole period, incidence was 5.4 per 100 000 among adults aged 18–64 years, and 82.6 per 100 000 among those aged ≥65 years. Among the former, incidence was up to 21 times higher in diabetics than non-diabetics. Among the elderly, incidence in diabetics was 2–3 times higher than in non-diabetics, and was higher than 300 per 100 000 throughout the period of observation.

Discussion

We found no epidemiological evidence of local transmission of the *magA*+ *rmpA*+ HV *K. pneumoniae* strain prior to the arrival of our patient in Canada, nor after his hospitalization. During the study period, there was no increase in the frequency of *K. pneumoniae* liver abscess and not a single case of *K. pneumoniae* meningitis or endophthalmitis. We can not rule out, however, the possibility that some inpatients became colonized with the HV strain, without developing clinical consequences. The exact whereabouts of the index patient before his arrival into Canada are uncertain: although he asserted that he had come directly from Algeria, a country not known to be endemic for HV *K. pneumoniae*, and had not visited Asia recently. He was, however, seeking asylum and would have had good reasons to conceal that he had passed through a third country. Recent publications from Algeria and Tunisia on *K. pneumoniae* infections focused on CTX-M β-lactamase-producing strains but did not report the HV phenotype; [13,14] however, the *rmpA*+ HV phenotype was already present in South Africa by 1996–1997 [15].

This is the first study measuring the population incidence of *K. pneumoniae* bacteraemia. We documented an 82% increase in incidence during the study period, and a dramatic age-related gradient. The aging of the population contributed to this rising incidence; the proportion of individuals aged ≥65 years increased from 13.1% to 15.3% during that interval, a relative increase of 17% [10]. Simultaneously, there

TABLE 3. Annual incidence of *Klebsiella pneumoniae* bacteraemia per 100 000 inhabitants in Sherbrooke, Canada

	1997–1998	1999–2000	2001–2002	2003–2004	2005–2006	2007
Total	10.2	12.2	15.5	15.6	17.8	18.7
Age groups						
<18 years						
All	0.0	1.6	0.0	1.7	9.9	6.6
18–64 years						
All	2.7	4.2	5.2	4.6	9.1	7.0
Non-diabetic	5.6	5.5	8.6	5.3	NA	NA
Diabetic	0.0	111.8	64.7	112.6	NA	NA
≥65 years						
All	67.3	71.7	94.1	93.7	73.1	93.4
Non-diabetic	108.1	113.2	167.9	151.8	NA	NA
Diabetic	335.1	358.4	317.2	401.6	NA	NA
Site of acquisition						
Community	3.5	4.2	4.5	6.1	3.7	5.3
Healthcare-associated	3.2	3.1	5.9	5.1	6.7	6.0
Hospital	3.5	4.9	5.2	4.4	7.4	7.3

NA, not available.

was, in Canada as elsewhere, an increase in the prevalence of diabetes mellitus, a condition strongly associated with *K. pneumoniae* infection. In Quebec, prevalence of diabetes among adults increased from 4.3% in 1997–1998 to 6.4% in 2003–2004, a 49% relative increase [16]. In Sherbrooke, from 1997 to 2004, prevalent cases of diabetes increased by 58% in individuals aged 18–64 years and by 41% among those aged ≥65 years; in 2004, prevalence of diabetes was 3.6% among the former and 14.3% in the latter group. During this period, there was no change in the accessibility to health care, or in the criteria used by physicians to diagnose diabetes. The incidence of *K. pneumoniae* bacteraemia remained fairly stable in each of the age- and diabetes-specific strata. Thus, increases in the number of diabetics to a large extent accounted for the secular changes in the incidence of *K. pneumoniae* bacteraemia. The age gradient may reflect exposure to the pathogen within healthcare settings, a higher frequency of biliary or urinary tracts anomalies, or senescence of the immune response.

In Taiwan, diabetes was found in 40% of patients with *K. pneumoniae* bacteraemia and 70% of those with liver abscess [2,3]. Elsewhere, one-fourth to one-half of patients with *K. pneumoniae* bacteraemia were diabetic [2,17–19]. Among our adult patients, 32% (45% in 2005–2007) were diabetic. Diabetes has complex impacts on immunity, notably an impairment of neutrophilic functions (chemotaxis, adherence, phagocytosis and intracellular killing) [20]. Streptozotocin-induced diabetes led to a higher mortality among mice experimentally infected with *K. pneumoniae* [21]. Phagocytosis of K1/K2 *K. pneumoniae* isolates by neutrophils is reduced among diabetic patients with poor glycaemic control compared with diabetics with adequate glycaemic control or healthy non-diabetics [22]. Diabetics are also more likely to develop infections caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, *S. agalactiae* and *Mycobacterium tuberculosis* [23], but this is the first time that a population impact of diabetes on any given infection has been documented.

Risk factors for mortality were similar to those reported in previous studies: hospital acquisition, pneumonia as the source, bacteraemia of unknown source, inappropriate treatment [23–25]. In previous reports, nosocomial bacteraemia were more likely to be caused by antibiotic resistant strains [25]. In our population, resistance to third-generation cephalosporins and ciprofloxacin was remarkably uncommon; the higher mortality among nosocomial cases may result from co-morbidities, whereas polymicrobial bacteraemia may reflect a more severe underlying process. Of note, diabetes was not associated with a higher mortality, in ours as well as in previous studies.

In conclusion, we have documented the second case of *magA+ rmpA+* hypermucoviscosity phenotype *K. pneumoniae* infection in Canada, probably imported from North Africa, but without epidemiological evidence of local transmission. We measured for the first time the population incidence of *K. pneumoniae* bacteraemia, which increased by 82% between 1997 and 2007, to some extent a consequence of the huge increase in the number of adult diabetics. Sedentary life style, chronic diseases and infections may interact in the trend.

Transparency Declaration

Acquisition of data concerning the population of diabetics in the Sherbrooke area was funded through the GEIODE network of centres of excellence. Other funding was departmental. The authors declare no conflicts of interest.

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